



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2018

Prospective evaluation of medication-related clinical decision support over-rides in the intensive care unit

Wong, Adrian ; Amato, Mary G ; Seger, Diane L ; Rehr, Christine ; Wright, Adam ; Slight, Sarah P ;
Beeler, Patrick E ; Orav, E John ; Bates, David W

Abstract: **BACKGROUND:** Clinical decision support (CDS) displayed in electronic health records has been found to reduce the incidence of medication errors and adverse drug events (ADE). Recent data suggested that medication-related CDS alerts were frequently over-ridden, often inappropriately. Patients in the intensive care unit (ICU) are at an increased risk of ADEs; however, limited data exist on the benefits of CDS in the ICU. This study aims to evaluate potential harm associated with medication-related CDS over-rides in the ICU. **METHODS:** This was a prospective observational study of adults admitted to any of six ICUs between July 2016 and April 2017 at our institution. Patients with provider-overridden CDS for dose (orders for scheduled frequency and not pro re nata), drug allergy, drug-drug interaction, geriatric and renal alerts (contraindicated medications for renal function or renal dosing) were included. The primary outcome was the appropriateness of over-rides, which were evaluated by two independent reviewers. Secondary outcomes included incidence of ADEs following alert over-ride and risk of ADEs based on over-ride appropriateness. **RESULTS:** A total of 2448 over-ridden alerts from 712 unique patient encounters met inclusion criteria. The overall appropriateness rate for over-rides was 81.6% and varied by alert type. More ADEs (potential and definite) were identified following inappropriate over-rides compared with appropriate over-rides (16.5 vs 2.74 per 100 over-ridden alerts, Fisher's exact test $P < 0.001$). An adjusted logistic regression model showed that inappropriate over-rides were associated with an increased risk of ADEs (OR 6.14, 95% CI 4.63 to 7.71, $P < 0.001$). **CONCLUSIONS:** Approximately four of five identified CDS over-rides were appropriately over-ridden, with the rate varying by alert type. However, inappropriate over-rides were six times as likely to be associated with potential and definite ADEs, compared with appropriate over-rides. Further efforts should be targeted at improving the positive predictive value of CDS such as by suppressing alerts that are appropriately over-ridden.

DOI: <https://doi.org/10.1136/bmjqs-2017-007531>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-158995>

Journal Article

Accepted Version

Originally published at:

Wong, Adrian; Amato, Mary G; Seger, Diane L; Rehr, Christine; Wright, Adam; Slight, Sarah P; Beeler, Patrick E; Orav, E John; Bates, David W (2018). Prospective evaluation of medication-related clinical decision support over-rides in the intensive care unit. *BMJ Quality and Safety*, 27(9):718-724.

DOI: <https://doi.org/10.1136/bmjqs-2017-007531>

Prospective Evaluation of Medication-related Clinical Decision Support Overrides in the Intensive Care Unit

ABSTRACT

Introduction

Clinical decision support (CDS) displayed in electronic health records (EHRs) has been found to reduce the incidence of medication errors and adverse drug events (ADEs). Recent data suggested that medication-related CDS alerts were frequently overridden, often inappropriately. Patients in the intensive care unit (ICU) are at an increased risk of ADEs; however, limited data exist on the benefits of CDS in the ICU. This study aims to evaluate potential harm associated with medication-related CDS overrides in the ICU.

Methods

This was a prospective observational study of adults admitted to any of 6 ICUs between July 2016 and April 2017 at our institution. Patients with provider-overridden CDS for dose (orders for scheduled frequency and not pro re nata), drug-allergy, drug-drug interaction, geriatric, and renal alerts (contraindicated medications for renal function or renal dosing) were included. The primary outcome was the appropriateness of overrides, which were evaluated by two independent reviewers. Secondary outcomes included incidence of ADEs following alert override and risk of ADEs based on override appropriateness.

Results

A total of 2448 overridden alerts from 712 unique patient encounters met inclusion criteria. The overall appropriateness rate for overrides was 81.6% and varied by alert type. More ADEs (potential and definite) were identified following inappropriate overrides compared to appropriate overrides (16.5 vs. 2.74 per 100 overridden alerts, Fisher's exact test $p < 0.001$). An adjusted logistic regression model showed that inappropriate overrides were associated with an increased risk of ADEs (OR 6.14, 95% CI 4.63-7.71, $p < 0.001$).

Conclusions

Approximately four of five identified CDS overrides were appropriately overridden, with the rate varying by alert type. However, inappropriate overrides were six times as likely to be associated with potential and definite ADEs, compared to appropriate overrides. Further efforts should be targeted at improving the positive predictive value of CDS such as by suppressing alerts that are appropriately overridden.

Keywords: Adverse drug event; clinical decision support; critical care; informatics; patient safety; quality of care

INTRODUCTION

Adverse drug events (ADEs) are injuries resulting from a medication, which may result from medication errors. Given their association with increased hospital length of stay, costs, and morbidity and mortality, efforts have been made to reduce these often preventable events.[1-3] Medication-related clinical decision support (CDS) has been identified as an effective way to reduce medication errors, along with the introduction of computerized provider order entry.[4,5] However, literature regarding the proportion of CDS alerts that are overridden including those that are overridden inappropriately is increasing.[6,7] Therefore, studies evaluating the association between appropriateness of CDS overrides and ADEs are needed, though relatively few have been done.[8]

One patient population that is particularly susceptible to ADEs is intensive care unit (ICU) patients, who are at increased risk compared to other hospitalized patients because they receive a large number of medications, including many high-risk medications; have altered pharmacokinetics and organ systems; and a relatively increased length of stay.[9-11] Two prospective cohort studies identifying ADEs in the ICU found that they were relatively common (30.6 – 96.5 per 1,000 patient days), and associated with increased morbidity.[12,13] A study performed at our institution using our legacy, homegrown electronic health record (EHR) system found that inappropriately overridden CDS alerts were associated with an increased risk of ADEs.[8] However, this study had limitations including that it was retrospective, had a small sample size, and there were concerns about generalizability as it was done within a homegrown system. Given the lack of published data regarding harms associated with medication-related CDS overrides and the potential increased risk in ICU patients, our objective was to characterize these issues in a commercial EHR. By identifying the extent of harm associated with these CDS

alert overrides, we will identify ways to improve current CDS alert systems, allowing providers to focus their attention on clinically pertinent alerts.

MATERIALS AND METHODS

We performed a prospective, observational study evaluating medication-related CDS alert overrides by providers (anesthesiologist, fellow, nurse practitioner, physician, physician assistant, resident). Alert overrides were generated between July 2016 and April 2017 from patients admitted to one of the following ICUs at XXX: medical (n=2), neurology (n=2) or surgical (n=2). Alert logic was sourced from First Databank (First Databank, South San Francisco, CA, USA). Clinical decision support also included order sentences and default doses, although these were inconsistent across medications in regards to their function and clinical utility.

Five computerized alert types that are frequent and of clinical significance in the ICU patient population were included: dose, drug-allergy, drug-drug interaction (DDI), geriatric and renal. Specific alerts targeted within each alert type were based on a 6-month pilot study (October 2015 to May 2016) evaluating alert overrides. Factors considered in choosing the alerts to evaluate included clinical experience, frequency, and severity of harm. Further details on the specific alerts chosen may be found in the Supplementary File (Appendix A). All alerts that were evaluated in this study were presented to providers at the time of order signing (i.e., not informational) and required an action by the provider to continue with the order (i.e., override). Therefore, the inclusion criteria for this study were 1) Patient was admitted to one of 6 ICUs within our institution; 2) The alert was one of five alert types and was in one of the subcategories, found in Appendix A; 3) The alert fired on a patient within our study time period (July 2016 to April 2017); and 4) The alert was presented to the provider at the time of order

signing. For geriatric alerts, only 'contraindicated' alerts were included as only these were provided to multiple providers (i.e., not only the initial ordering provider). Geriatric 'precaution' alerts were only presented to the ordering provider and were therefore, excluded. Exclusion criteria included patients with a hospital length of stay of <24 hours after the override to allow for adequate time to evaluate potential harm.

Data collection included the patient's age and gender, Sequential Organ Failure Assessment score at the time of the patient's first override included in this study, the type of hospital and ICU admission, type of ICU, hospital and ICU length of stay, and documented rationale for override.[14] Acute kidney injury was defined using guidelines.[15] The primary outcome was the appropriateness of the override, assessed by two independent reviewers with a set of predetermined criteria specific for each type of alert. Secondary outcomes included the documented reason for override (which was only required for drug-allergy alerts), the incidence of ADEs following alert override and association of override appropriateness with ADE. This study was approved by the XXX Institutional Review Board.

Appropriateness Evaluation

Criteria for appropriateness were created using previously published data, including guidelines as well as clinical experience of a multidisciplinary group.[13,16] Criteria were specific for alert categories and modified until a consensus was reached. Parameters included if the medication was being used for comfort measures only (i.e, hospice), gender and baseline QTc (defined as value prior to initiation of medications from alert), past receipt of medication and documented reactions (if present), if the medication was a home medication and no documented adverse reactions had occurred from its use. For patients administered medications for comfort measures, these overrides were identified as appropriate if they were used at

reasonable doses. An example of our appropriateness criteria for geriatric alerts may be found in the Supplementary File (Appendix B). Appropriateness was independently evaluated for all overridden alerts by two clinical pharmacists (one with significant experience in critical care and medication safety, one with significant experience in medication safety). The inter-rater agreement for appropriateness was determined with a Cohen's κ statistic. Disagreements were resolved by discussions between the two independent reviewers. If consensus was not achieved, a third experienced reviewer (physician with significant experience in medication and patient safety) was consulted.

ADE Evaluation

To evaluate for ADEs, we performed patient chart reviews on overrides in which the patient received the overridden alert's specific medication(s). An ADE was defined as an injury occurring from use of a medication. The period of evaluation started after the override and continued for the time that the medication(s) remained active in the patient's medication orders, which could have persisted to hospital discharge in some cases. ADEs that were included were specific to the overridden alert. Data relevant to an ADE, such as laboratory reports, medication orders and patient notes documented by nurses or providers, were abstracted and summarized by one reviewer. These data were blinded (i.e., appropriateness of override was not provided) and forwarded to two independent reviewers to determine the likelihood (no ADE, possible ADE, definite ADE) and severity of the ADE, regardless of likelihood (significant, serious, life-threatening). A definite ADE was defined as harm that only could have occurred due to use of the medication, while a possible ADE was an ADE which could have resulted from other causes (e.g., delirium from ICU illness or from medication use). We included for example instance in which the QT was prolonged to over 0.50. Definitions for severity of the ADE were based on

previous work by members of our study team.[11] An example of a life-threatening ADE was the requirement for cardiopulmonary resuscitation to sustain life, while a serious ADE was excessive sedation. If consensus was not achieved, a third experienced reviewer (physician) was consulted. Study personnel had undergone training based on guidance developed by the XXX, which has been used in previous studies and previously described.[17]

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. Fisher's exact test was used to compare categorical variables (rate of override by alert type, appropriateness of overrides by alert type and rate of ADEs by appropriateness). Multivariable logistic regression was performed to assess the association between the appropriateness of an override and the risk of ADEs (possible and definite). The model was adjusted for the following predefined patient baseline characteristics: age, gender, Sequential Organ Function Assessment (SOFA) score, which may be potential confounders for ADEs. These confounders were chosen based on our expert knowledge. A post hoc multivariable linear regression was performed to assess the association between the appropriateness of an override and the ICU length of stay. This model was also adjusted for potential confounders, as above. A p-value of <0.05 was considered significant. Statistical analysis was completed using R 3.3.3 (R Core Team, Vienna, Austria).

RESULTS

A total of 24231 alerts in the parent alert types (dose, drug-allergy, DDI, geriatric, renal) were presented to staff from 3312 unique patient encounters, with an overall override rate of 88.5%. The override rate varied by alert type (dose: 96.8%, drug-allergy: 83.6%, DDI: 91.9%, geriatric: 2.3%, renal: 97.1%; $p < 0.001$). For this study, 2448 overridden alerts met inclusion

criteria (10.1% of total alerts). Patient demographics of unique patient encounters with alerts that met inclusion criteria (n=712) are detailed in Table 1.

Table 1. Patient demographics

Mean age, y (SD)	62.4 (16.8)
Female, n (%)	361 (50.7)
Hospital admission type, n (%)	
Medical	547 (76.8)
Surgical	165 (23.2)
ICU admission type, n (%)	
Medical	520 (73.0)
Surgical	192 (27.0)
Initial ICU admitted to, n (%)	
Medical	368 (51.7)
Neurology	146 (20.5)
Surgical	198 (27.8)
Median SOFA, (IQR)	4 (3, 7)
Median ICU LOS, d (IQR)	3.9 (2.1, 8.8)
Median hospital LOS, d (IQR)	11.2 (5.4, 20.4)
Deceased, n (%)	157 (22.1)

ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; SD = standard deviation

Characteristics of Alert Types

For drug-allergy overrides, most were due to a definite match between the ordered medication and documented allergen (n=248, 89.5%). The most common override was due to acetaminophen for the definite match overrides (n=99, 39.9%). Of these overrides, only 10 (10.1%) were due to an acetaminophen-only allergy, while the remainder was due to documented allergies of acetaminophen in combination with other medications (e.g., oxycodone). Of the 29 potentially life-threatening drug-allergy overrides, anaphylaxis was the most common documented reaction to the allergen (n=13, 44.8%). Acetaminophen was again the most common medication ordered (n=10, 34.5%), with these overrides due to a documented allergy of a combination of acetaminophen with other medications. The most commonly documented

override reason was 'Will monitor' (n=115, 46.4%) and 'Patient tolerated before' (n=11, 37.9%) for the definite allergy and life-threatening allergy overrides, respectively.

The evaluation of DDI overrides showed that most alerts were triggered by medication combinations that increase the risk of QTc-prolongation (n=1569, 86.9%), with haloperidol the most common medication alerted on (n=716, 39.6%). Subcutaneous heparin (n=18, 50.0%), simvastatin (n=22, 34.4%), and sulfamethoxazole-trimethoprim (n=44, 55.7%) were the most common medications for the anticoagulant, 'contraindicated,' and 'other' DDI alert types, respectively. A total of 38 patients (2.1%) were continued on home medications that resulted in a medication alert. Override reasons were not required and infrequently used (n=504, 27.9%), with 'Will monitor' the most common amongst all DDI overrides (n=342, 67.9%).

For the dose alerts, benzodiazepines accounted for most of the overrides (n=31, 75.6%), with lorazepam the most common (n=23, 74.2%). Hold parameters, which are input by providers, (e.g., medication should not be administered if a parameter such as low blood pressure exists) for the medication order were used in only 18 of the alerts (43.9%). 'Will monitor' was the most common override reason entered (n=8, 66.7%).

Regarding the geriatric alerts, chlorthalidone and nifedipine were the most common medications alerted on (n=6 each, 28.6%). 'Patient tolerated before' and 'Will monitor' were the most common override reasons provided (n=3 each, 42.9%).

For the renal alerts, electrolytes accounted for most overrides (total: n=154, 50.8%; magnesium sulfate: n=24, potassium chloride: n=130). Most alerts were due to acute kidney injury (AKI) (n=170, 56.1%), with 88 of these alerts (51.8%) indicative of improving AKI and 3 alerts in patients undergoing continuous renal replacement therapy. A total of 43 alerts (16.3%) were due to continuation of a home medication. Of these alerts, 7 (14.0%) had an increasing

trend to the patient's serum creatinine suggestive of developing kidney injury, while 13 (30.2%) were in hemodialysis-dependent patients. Of those overrides that had an override reason, 'Will monitor' was the most commonly documented rationale (n=47, 71.2%).

Appropriateness of Overrides

The overall appropriateness rate was 81.6% (Table 2). The κ for the criteria agreement of appropriateness was 0.89 (95% CI 0.85-0.93) indicating almost perfect agreement, with a percent agreement of 92.1%.

Table 2. Rate of appropriateness of overrides by alert type

	Allergy (n=277)	DDI (n=1806)	Dose (n=41)	Geriatric (n=21)	Renal (n=303)
Appropriate, n (%)	231 (83.4)	1481 (82.0)	18 (43.9)	3 (14.3)	265 (87.5)

DDI = drug-drug interaction

The appropriateness rate differed significantly by alert type ($p < 0.001$). Evaluation of appropriateness rates for the drug-allergy and DDI alert subtypes (Table 3) showed that overrides of potentially life-threatening drug-allergy alerts were appropriate approximately 70% of the time.

Table 3. Rate of appropriateness of overrides by alert subtype

Alert type/subtype	Number appropriate, (%)
Allergy	
Definite match	221 (89.1)
Definite match and life-threatening	20 (69.0)
DDI	
Amiodarone-digoxin	58 (100)
Anticoagulants	24 (66.7)
Contraindicated	40 (62.5)

QTc-prolongation	1295 (82.5)
Other	64 (81.0)

DDI = drug-drug interaction

Appropriateness of DDIs overrides differed significantly between subtypes, with amiodarone-digoxin overrides always being appropriately overridden.

Adverse Drug Events

A total of 1636 overridden alerts resulted in medication administration(s) to the patient (66.8% of study sample) and 56 resulted in an ADE (potential or definite) (see Supplementary File, Appendix C). The κ for ADE determination was 0.93 (95% CI 0.90-0.96) indicating excellent agreement, with a percent agreement of 95.1%. Most ADEs were considered to be ‘potential’ (n=52, 92.9%). Three out of four ‘definite ADEs’ were a result of a ‘definite’ drug-allergy match alert such as vancomycin resulting in red-man syndrome. Most ADEs were serious (n=50, 89.3%), with altered mental status (n=10, 20.0%) and QTc-prolongation (n=36, 72.0%) the most common ADEs encountered. No ADEs resulted from the anticoagulant DDIs. Only one ADE resulted from continuation of a home medication (geriatric alert, amitriptyline).

There was one life-threatening event, potentially an ADE and possibly related to an override. This occurred in a patient with a baseline QTc of 535 msec at hospital admission. The override was for trazodone (new medication) in conjunction with ritonavir (home medication), while the patient was being administered quetiapine (new medication) for agitation. The patient suffered a cardiac arrest with ventricular fibrillation and ultimately died a few days later.

As only medications that were administered to the patient could have been evaluated for ADEs, Table 4 details the number of alerts that resulted in medication administration and the rate of ADEs by appropriateness of override. Table 4.

Table 4. Rate of adverse drug events by appropriateness of override

	Allergy (n=207)	DDI (n=1170)	Dose (n=26)	Geriatric (n=11)	Renal (n=222)	Total (n=1636)
Appropriate and administered, n (%) ^a	181 (87.4)	959 (82.0)	9 (34.6)	2 (18.2)	209 (94.1)	1360 (83.1)
Appropriate + ADE, n (%) ^b	1 (0.6)	19 (2.0)	1 (11.1)	0	0	21 (1.5)
Inappropriate and administered, n (%) ^a	26 (12.6)	211 (18.0)	17 (65.4)	9 (81.8)	13 (5.9)	276 (16.9)
Inappropriate + ADE, n (%) ^b	3 (11.5)	24 (11.4)	3 (17.6)	1 (11.1)	4 (30.8)	35 (12.7)

^a Percentage based on number of override by alert category

^b Percentage based on number of overrides that resulted in medication administration to the patient

ADE = adverse drug event; DDI = drug-drug interaction

There was a significant increase in the rate of ADEs with inappropriate overrides, compared to appropriate overrides. The unadjusted logistic regression found that inappropriate overrides were associated with an increased risk of ADEs (OR 6.13, 95% CI 4.64-7.69, $p < 0.001$), with similar findings from the adjusted logistic regression (OR 6.14, 95% CI 4.63-7.71, $p < 0.001$).

Inappropriate overrides were associated with an increased ICU length of stay of 2.25 days (95% CI 0.52-3.98, $p = 0.011$).

DISCUSSION

We evaluated the appropriateness of medication-related CDS overrides in the ICU and ADEs associated with these overrides. A significant proportion of medication-related CDS alerts are overridden in the ICU (88.5%). Based on the overrides that were studied, appropriateness was also high (81.6%) and varied significantly by the type of alert, with drug-allergy overrides being commonly appropriately overridden, whereas geriatric alerts were frequently inappropriately overridden. Inappropriate overrides were associated with a six-fold increased risk

of ADEs (potential and definite), compared to appropriately overridden alerts. Appropriateness rates were in line with the published literature, likely due to the alert types studied and the close monitoring that occurs in the ICU.[6,13]

Our institution transitioned from our legacy EHR to a commercial EHR in May 2015. Efforts had been continually made to our legacy system to improve available clinical CDS, including increasing its positive predictive value (PPV) to limit potential alert fatigue.[18,19] With the transition to the commercial EHR, we found a significant increase in alerts by approximately 5-fold, along with a significant increase in override rates of certain alert types.[20] Potential reasons for this significant increase were the removal of our tailored CDS as well as the presentation of CDS alerts at the time of order signing, instead of at the time of ordering as in the legacy system. Evaluation of appropriate overrides to modify available EHR systems and knowledge bases is of importance to increase the clinical relevance of presented CDS alerts. The removal of this tailoring due to our EHR system transition reduced this PPV of our CDS alerts.

Discussion of Specific Alert Types

Based on previous experience in evaluating drug-allergy overrides, we focused on two specific subtypes that were of particular clinical interest. The appropriateness of the overrides differed by the subtype, with definite matches commonly appropriately overridden (89.1%), while life-threatening alerts were often appropriately overridden (69.0%) but to a decreased extent compared to definite matches. A match between the ordered medication and the documented allergen can increase the PPV of these alerts. However, the premise of combination products (e.g., oxycodone-acetaminophen) adds complexity to provider documentation of these allergies.

DDIs accounted for the majority of studied CDS overrides, due to a large number of QTc-prolonging medication combinations. In evaluating the subtypes of the DDI alerts, the amiodarone-digoxin and anticoagulant subtypes were of particular interest. None of the amiodarone-digoxin overrides were inappropriate, and no anticoagulant DDIs resulted in ADEs. The lack of ADEs associated with anticoagulants, which are considered to be high-risk medications, is surprising but was often due to discontinuation of one anticoagulant at the same time as ordering another.[21] Our CDS system believed that the to-be-discontinued anticoagulant was still an active order, when in fact it was in the process of being discontinued. In evaluating the ‘contraindicated’ DDIs, overrides were frequently appropriate as simvastatin and a metabolism-inhibitor were the most common DDI combinations, which were often not reflective of the dose threshold for simvastatin that is recommended in guidelines.[22] The low rate of ADEs associated with this DDI subtype was due to the large number of simvastatin DDIs. It would be expected to require more time than a typical ICU stay to occur (i.e., myopathy/rhabdomyolysis).

In evaluating the dose alerts, it was concerning that only 43.9% of these orders had any hold parameters associated with the medication. Of the 4 ADEs that potentially resulted from the overrides, only 1 had a hold parameter associated with the order.

For geriatric alerts, an interesting finding was that the acceptance of these alerts (97.5%) was much more common than reported in the literature.[8] This acceptance rate was also significantly greater than the rest of the studied alert types. Potentially, these alerts are the most specific to a patient, resulting in the highest provider acceptance. This is supported by the high rate of inappropriate overrides found in this study (85.7%). The small number of overridden alerts was because only ‘contraindicated’ alerts were included in this study because they were

presented to all providers. ‘Precaution’ alerts were only presented to the original ordering provider and not to subsequent providers in cases of reordering the same medication or changing the dose. The renal alerts contrasted previous findings within our institution, when they had been tailored to be as specific as possible.[18] In the commercial database, electrolyte alerts accounted for most of the overrides (50.8%), whereas no such alerts were active in our legacy system. These were clinically insignificant alerts, resulting in a high rate of appropriate overrides.

Recommendations to Improve Clinical Decision Support

One finding that is noted in the results of this study is the evaluation of what CDS alerts exist within an institution. Malfunctions of CDS have been studied in the literature, which has identified that they may be widespread and may exist for long time periods due to lack of investigation into this matter.[23] A few of the malfunctions that were encountered during this study period were focused on the actual medication ordered compared to what the CDS believed was ordered (e.g., simvastatin as previously mentioned). This illustrates the need for evaluation of CDS, especially in the time period immediately following EHR implementation, as we did in our institution.

A general improvement would be linking the override reason to an appropriate intervention. For example, when “Will monitor” is chosen as the override reason for an amiodarone-digoxin DDI, an order for a serum digoxin level would be made. This could become more specific by evaluating additional parameters such as the dose and renal function in determining the date and time of the serum digoxin level order.

Although it may be difficult to determine which component of a combination product may lead to an allergy, the use of previous tolerance to a component would likely be able to reduce the alert burden. This could be accomplished through the use of machine learning and

natural language processing that could more accurately determine culprit medications.[24,25] Additionally, our EHR and CDS system can differentiate between a true medication allergy and that of intolerance. By differentiating how CDS presents a true medication allergy (e.g., anaphylaxis) to an intolerance (e.g., nausea), providers may value CDS more (i.e., more correctly respond), which in turn may reduce the incidence of inappropriate overrides. For dose alerts, incorporation of a hold parameter could potentially prevent ADEs from occurring. Removal of renal alerts for one-time orders of electrolytes as long as the serum lab value (within a reasonable amount of time) was within a certain range, would help alleviate a significant portion of these alerts.[26]

Limitations

Our study has several limitations. First, this study was completed at a single center based on only one commercial EHR/database and therefore, may not necessarily be applicable to other institutions. However, data suggests that this commercial EHR is implemented in a significant portion of the market.[27] Second, we may not have exhaustively evaluated factors that the provider may have considered in determining the decision to override a CDS alert. Nevertheless, we made considerable efforts to evaluate the appropriateness of overrides and subsequent ADEs on a case-by-case basis, formulation of criteria using a multidisciplinary expert team, and the use of independent adjudicators. Third, we are unable to determine causality of our findings, only association, given the nature of our study design. Fourth, we were time limited as we only evaluated for ADEs that occurred during the hospital stay. Patient may have remained on some medications that were ordered upon hospital discharge, which would be important for ADEs that are expected to take a longer time to manifest. Fifth, we were dependent on clinical documentation for the determination of ADEs, which might have limited our findings. Finally,

we included in our definition of ADE some things such as QT prolongation which other studies might or might not.

CONCLUSION

Approximately four of five identified CDS overrides were appropriately overridden, though the rate varied substantially by alert type. Inappropriate overrides were six times as likely to be associated with an ADE (potential and definite) compared to appropriate overrides, confirming that decision support can identify clinically important situations. Further efforts should be targeted at improving the positive predictive value of CDS in a number of ways, including by following human factors principles in alert presentation, by suppressing alerts that are appropriately overridden, by using clinical information about individual patients to improve the likelihood that the alerts will be appropriate, and by using techniques such as artificial intelligence to help determine which alerts to present.

COMPETING INTERESTS

XXX reported receiving equity from XXX, which makes software to support clinical decision-making in intensive care; being named as coinventor on patent XXX held by XXX on the use of decision support software for medical management, licensed to the XXX, and holding a minority equity position in XXX, which develops web-based decision support for radiology test ordering; consulting for XXX, which makes patient safety monitoring systems; receiving equity and cash compensation from XXX, a company focused on intelligence systems for electronic health records; receiving cash compensation from XXX, which is a not-for-profit incubator for health IT startups; receiving equity from XXX, which makes software to support evidence-based clinical decisions, from XXX, which makes software to help patients with chronic diseases, and from XXX, which takes clinical data and produces deidentified versions of it. The remaining authors have disclosed that they do not have any conflicts of interest.

FUNDING

This study was funded by CRICO, Risk Management Foundation (Boston, MA).

REFERENCES

1. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 1991;324:377-384.
2. Classen DC, Pestotnik SL, Evans RS, et al. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1997;277:301-6.
3. Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. *JAMA* 1997;277:307-11.
4. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA* 1998;280:1311-6.
5. Bates DW, Teich JM, Lee J, et al. The impact of computerized physician order entry on medication error prevention. *J Am Med Inform Assoc* 1999;3:13-21.
6. Lin CP, Payne TH, Nichol P, Hoey PJ, Anderson CL, Gennari JH. Evaluating clinical decision support systems: monitoring CPOE order check override rates in the Department of Veterans Affairs' Computerized Patient Record System. *J Am Med Inform Assoc* 2008;15:620-6.
7. Nanji KC, Slight SP, Seger DL, et al. Overrides of medication-related clinical decision support alerts in outpatients. *J Am Med Inform Assoc* 2014;21:487-91.
8. Wong A, Amato MG, Seger DL, et al. Evaluation of medication-related clinical decision support overrides in the intensive care unit. *J Crit Care* 2017;39:156-61.
9. Cullen DJ, Sweitzer BJ, Bates DW, et al. Preventable adverse drug events in hospitalized patients: a comparative study of intensive care and general care units. *Crit Care Med* 1997;25:1289-97.
10. Rothschild JM, Landrigan CP, Cronin JW, et al. The Critical Care Safety Study: the incidence and nature of adverse events and serious medical errors in intensive care. *Crit Care Med* 2005;33:1694-1700.

11. Morimoto T, Sakuma M, Matsui K, et al. Incidence of adverse drug events and medication errors in Japan: the JADE study. *J Gen Intern Med* 2011;26:148-53.
12. Nazer LH, Hawari F, Al-Najjar T. Adverse drug events in critically ill patients with cancer: incidence, characteristics, and outcomes. *J Pharm Pract* 2014;27:208-13.
13. Ohta Y, Sakuma M, Koike K, Bates DW, Morimoto T. Influence of adverse drug events on morbidity and mortality in intensive care units: the JADE study. *Int J Qual Health Care* 2014;26:573-8.
14. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707-10.
15. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int* 2012;2:1-138.
16. American Geriatrics Society 2015 Beers Criteria Update Expert Panel: American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 2015;63:2227-46.
17. Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. *Qual Saf Health Care* 2004;13:306-14.
18. Chertow GM, Lee J, Kuperman GJ, et al. Guided medication dosing for inpatients with renal insufficiency. *JAMA* 2001;286:2839-44.
19. Peterson JF, Kuperman GJ, Shek C, Patel M, Avorn J, Bates DW. Guided prescription of psychotropic medications for geriatric inpatients. *Arch Intern Med* 2005;165:802-7.
20. Wong A, Wright A, Seger DL, Amato MG, Fiskio JM, Bates DW. Comparison of overridden medication-related clinical decision support in the intensive care unit between a commercial system and a legacy system. *Appl Clin Inform* 2017;8:866-79.
21. ISMP List of High-Alert Medications in Acute Care Settings. Institute for Safe Medication Practices website. <https://www.ismp.org/tools/institutionalhighAlert.asp>. Updated 2014. Accessed July 31, 2016.
22. Food and Drug Administration. FDA Drug Safety Communication: important safety label changes to cholesterol-lowering statin drugs. Food and Drug Administration website. Available at: <https://www.fda.gov/Drugs/DrugSafety/ucm293101.htm>. Updated February 28, 2012. Accessed August 20, 2017.
23. Wright A, Hickman TT, McEvoy D, et al. Analysis of clinical decision support system malfunctions: a case series and survey. *J Am Med Inform Assoc* 2016;23:1068-76.
24. Goss FR, Plasek JM, Lau JJ, Seger DL, Chang FY, Zhou L. An evaluation of a natural language processing tool for identifying and encoding allergy information in emergency department clinical notes. *AMIA Annu Symp Proc* 2014;2014:580-8.
25. Hammann F, Gutmann H, Vogt N, Helma C, Drewe J. Prediction of adverse drug reactions using decision tree modeling. *Clin Pharm Ther* 2010;88:52-9.
26. Eschmann E, Beeler PE, Schneemann M, Blaser J. Developing strategies for predicting hyperkalemia in potassium-increasing drug-drug interactions. *J Am Med Inform Assoc* 2017;24:60-6.

27. Office of the National Coordinator for Health Information Technology. Hospital EHR Vendors. Available at: <https://dashboard.healthit.gov/quickstats/pages/FIG-Vendors-of-EHRs-to-Participating-Hospitals.php>. Updated September 2016. Accessed May 1, 2017.